REMARKS

Upon entry of the foregoing amendment, claims 1-53 will be pending. Claims 1 and 22 have been amended and claim 54 has been canceled without prejudice. Applicant reserves the right to pursue the subject matter relating to claim 54 in a divisional application. Support for the amendment of claim 1 can be found, for example, at page 24, lines 12-14 and lines 22-24. Support for the amendment of claim 22 is found, *e.g.*, at page 38, line 31 through page 39, line 10.

Counsel thanks Examiners Holleran and Caputa for the courtesy of a personal interview held on March 29, 2001. As discussed in the interview, Applicant believes that, upon consideration of the foregoing amendments and following remarks, the Examiner will withdraw the remaining rejections. Accordingly, a timely notice of allowance is solicited.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claim 54 under 35 U.S.C. § 102(b) as anticipated by Bosslet *et al.* The Examiner has stated that claim 54 will not be accorded the filing date of the grandparent application (07/182,623) and, therefore, maintains that Bosslet qualifies as prior art against this claim. In order to expedite prosecution of the instant application—and without acquiescing to the Examiner's position—Applicant has canceled claim 54 without prejudice and reserves the right to pursue the subject matter of claim 54 in a divisional application. Accordingly, the rejection is now moot.

Rejection under 35 U.S.C. § 103(a)

Old Grounds of Rejection:

The Examiner has rejected claims 12, 14, and 15 under 35 U.S.C. § 103(a) as obvious over Sharma *et al.* (Sharma), Blakey *et al.* (Blakey), or Bagshawe *et al.* (Bagshawe) in view of Martinis *et al.* (Martinis). Each of these rejected claims provides that the enzyme can be "caroboxypeptidase G2" (CPG2). It is true that Sharma, Blakey and Bagshawe disclose this enzyme. However, none of these references—either alone or in combination with Martinis—supports a case of *prima facie* case of obviousness. Accordingly, Applicant traverses the rejection on the merits, for the reasons that follow.

To establish a *prima facie* case of obviousness, the Examiner must show not only that the art evidences a motivation to have combined the references, as posited, but also that the combination suggests all recited elements. *See* MPEP § 2142. Here, the prior art does not teach or suggest all of the claimed elements. Furthermore, there is no motivation to combine any of the primary references (*i.e.* Sharma, Blakey or Bagshawe) with Martinis. Moreover, even if a combination of the prior art could be interpreted to recite each feature of the rejected claims, there is no reasonable expectation of success in arriving at the claimed invention.

For instance, the prior art—either alone or in combination—does not teach:

> at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity... [and wherein] the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate *in situ*.

Sharma, Blakey, and Bagshawe separately teach a conventional covalent linkage between the CPG2 enzyme and an antibody (*See* Sharma at the sentence bridging pages 659 and 660; Blakey at page 3287, last full paragraph; and Bagshawe at page 700, last full paragraph). The Examiner acknowledges that none of these references teaches a method of employing the targeting of the enzyme to a target site, using multispecific antibodies. But, the Examiner then cites Martinis *et al.* as teaching these multispecific antibodies.

However, the prior art does not disclose or suggest the binding of CPG2 to a targeting protein *in situ*. That is, the prior art does not disclose or suggest a non-covalent linkage between CPG2 and a targeting protein, which is required by the rejected claims. Under MPEP § 2142, therefore, the obviousness rejection must fall.

Even if the Examiner could marshal evidence that it would have been obvious to bind an enzyme to a targeting protein, as required by the claims, this would not be sufficient to establish a *prima facie* case of obviousness. For instance, the prior art also would have to evince a motivation to combine such a teaching with the teachings of Martinis. This is true, since the Examiner cites Martinis to supply the teaching relating to multispecific antibodies. However, as shown below, Martinis teaches away from administering to a patient a targeting protein, followed by administering an enzyme that can form a non-covalent linkage with a portion of the targeting protein *in situ*.

It is true that Martinis teaches "immunodiagnostic and immunotherapeutic processes which employ antibodies having a dual specificity" (page 7, lines 9-11; 14-16). Martinis might suggest polydomas (bispecific antibodies), such as hybrid monoclonal antibodies that have dual specificity for two different antigenic determinants, and certain immunodiagnostic and immunotherapeutic applications. However, Martinis does not teach or suggest using a proagent-activating enzyme in the context of the present invention.

Instead, Martinis discloses only bispecific antibodies that bind to a target site and directly to a therapeutic or diagnostic agent. At page 6, lines 18-28, Martinis states:

> ...there are provided processes for immunodiagnosis and immunotherapy employing antibodies having a dual specificity. Generally these processes employ a monoclonal antibody or polyclonal antibodies having a first specificity against a target antigen and a second specificity against a substance, for example, another antigen or hapten, which permits a diagnosis to made of the target antigen or which permits delivery of, or is itself, an agent which is lethal to the target antigen or the tissue with which it is associated. (emphasis added).

According to Martinis, the "*other*" antigen or hapten in the above-quoted passage can be, itself, a therapeutic or diagnostic agent and, therefore, is not a precursor thereof. Therefore, the methods taught by Martinis would result in the circulation of therapeutic or diagnostic agents in already active form, thereby subjecting patients to potential side effects as a result of non-localized agents. Indeed, the Examiner characterizes Martinis as "target[ing] a cytotoxic agent to a target site as an alternative to targeting a cytotoxic agent..." (Office Action at p. 5, lines 11-12). Applicants respectfully urge, however, that an enzyme is not a cytotoxic agent. Accordingly, Martinis actually teaches away from the present invention, inasmuch as the teachings of Martinis are directed solely to direct administration of active agents.

Applicant respectfully submits that the present rejection is based on impermissible hindsight reconstruction, since the only reference that discloses the use of bispecific antibodies to specifically bind an enzyme and a target site *in situ* is the present application. Accordingly, Applicant respectfully urges the Examiner to withdraw the obviousness rejections.

New Grounds of Rejection

The Examiner has rejected claims 7 and 45 as obvious over Potter *et al.* in view of either Bosslet, Sharma *et al.* or Blakey *et al.* and further in view of Martinis *et al.* In response, Applicant submits that Potter does not make up for the deficiencies that exist in the applied prior art. The foregoing remarks adequately point out the deficiencies in each of these applied prior art references and Applicant hereby reasserts those deficiencies. Potter merely teaches that a carboxylesterase can activate a CPT-11 prodrug, which, upon activation, is toxic to cells expressing and secreting a carboxylesterase.

Again, Applicant submits that this rejection is based on impermissible hindsight reconstruction. Accordingly, a withdrawal of the rejection and a notice of allowance are solicited.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 22 and 23 under 35 U.S.C. § 112, second paragraph, as vague and indefinite. In response, Applicant has amended claim 22 and submits that the amendment overcomes the rejection. With regard to claim 23, the Examiner questions, "whether both substances are present at the target sight." In response, Applicant submits that claim 23 is not vague and indefinite and the rejection does not necessitate an amendment. Instead, Applicant respectfully directs the Examiner to claim 1, which employs the same language (*i.e.* "...substance produced by or associated with the target site and present at the target site") as the rejected language in claim 23. Since the language of Claim 1 is free of any 35 U.S.C. § 112, second paragraph rejections, Applicant submits that the corresponding language in claim 23 also satisfies 35 U.S.C. § 112, second paragraph, *a fortiori*.

If, however, the rejection is predicated on the requirement in claim 23 that the targeting protein comprises "at least two first binding sites...", Applicant refers to page 20 (lines 1-4), for example, which provides for:

> Coupling the bispecific antibody to a further antibody derivative that binds to the same or a different epitope of the same tumor-associated antigen or to a different tumor-associated antigen...

Coupled with the plain meaning of Claim 23 (*i.e.* "substance...[is] present at the target site), the specification illustrates that each "substance" would be present at its respective target sight..." Accordingly, a withdrawal of the rejection is requested.

Obviousness-type double patenting:

The Examiner has rejected claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, and 49-53 over claims 1-26 of U.S. Patent No. 5,851,527 on obviousness-type double patenting grounds. Applicants note that the rejection of claim 12 in this fashion is improper, inasmuch as the Examiner has argued that claim 12 cannot claim priority from the specification of the patent cited in the double patenting rejection, whereas claim 12 in fact is fully supported by the '527 patent disclosure. In any event, the terminal disclaimer appended hereto is believed to satisfy the requirements of 37 C.F.R. §§ 1.321 (b) and (c), and therefore overcomes the obviousness-type double patenting rejections. Accordingly, withdrawal of this rejection is respectfully urged.

Conclusion

In view of the foregoing, Applicant submits that all rejections and objections are overcome or are mooted and that the present claims are in condition for allowance. Early notice to that effect is earnestly solicited. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

May 14, 2001
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate *in situ*;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

22. (Amended) The method of claim 17, wherein the [prodrug comprises a polymer that is not acted on by the enzyme to which is attached at least one oligomer to which] polymer is attached to at least one oligomer, wherein the oligomer is conjugated to at least one molecule or ion of the therapeutic agent, wherein the oligomer is acted on by the enzyme, and wherein the polymer is not acted on by the enzyme.